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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/415,795	10/08/99	ZHOU	P HMV-043.01

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EXAMINER	
SLOBODYANSKY,E	
ART UNIT	**PAPER NUMBER**
1652	14

DATE MAILED: 08/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/415,795	Applicant(s) Zhou et al.
	Examiner Elizabeth Slobodyansky	Group Art Unit 1652

☒ Responsive to communication(s) filed on *May 29, 2001*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-35* is/are pending in the application.

Of the above, claim(s) *12, 13, and 16-35* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11, 14, and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-35 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, as it reads on SCF and SEQ ID NO: 4 in Paper No. 13 filed May 29, 2001 is acknowledged. The traversal is on the ground(s) that "no undue burden is placed upon the Examiner to search all Groups as listed in the Restriction Requirement (M.P.E.P. 803)" (page 1). This is not found persuasive because the examination of Groups I-IV would entail divergent consideration in addition to search of at least classes 435/69.7, 530/402 and 514/2, for example, search of which is not required for the examination of Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12, 13 and 16-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected species of Group I and nonelected Groups II-IV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

Claims 1-11, 14 and 15 are under consideration.

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed application 60/103,787, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph.

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. 37 CFR 1.821(d) requires the use of assigned sequence identifier in all instances where the description or claims of a patent application discuss sequences.

The following are examples of incompliance where sequence containing more than four amino acids or ten nucleotides are given without a sequence identifier: sequences shown on pages 73-77, 135, 136, 143, 144, etc.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-11, 14 and 15 are drawn to a method for targeting degradation of a polypeptide using a hybrid of a ubiquitin protein ligase polypeptide and a target polypeptide interaction domain *in vivo*.

The claims are directed to a genus of molecules described by function. The ubiquitin protein ligase polypeptide family, including an E3 ubiquitin protein ligase family, is a multigene family of proteins from any source. SCF (claim 5) is an ubiquitin protein ligase complex comprising Skp1, Cullin and F-box containing proteins) that is involved in cell-cycle control in *Saccharomyces cerevisiae*. Three different SCF complexes are known in *S. cerevisiae* (see, for example, Skowya et al., form PTO-1449). The core of SCF complexes comprises SKP1p and Cdc53p. The specificity of the individual SCF complexes is conferred by the F-box proteins, Cdc4p, Grrp or Met30p. The Skp/Cdc53/Cdc4 complex in association with Cdc34 ubiquitinates Sic1p (Skowya et al., *supra*). Cdc4 is also auto-ubiquitinated by the SCF^{Cdc4p} complex (the specification, page 133). The specification teaches a method of use of a hybrid of Cdc4 with LTP and E7N (page 135) to degrade pRB when both the hybrid and pRB were

expressed in *S. cerevisiae* Y81 cells. The specification further teaches a method of use of a hybrid of a human analog of Cdc4, βTrCP, with E7N (pages 138-139) to degrade the endogenous protein, p107, when expressed in human C33A cells (Figure 11, page 140). Therefore, the specification teaches a method of use based on the use of a single representative of ubiquitin ligase complex, SCF. The method is based on the use of Cdc4 and its human analog, βTrCP, for degradation of a polypeptide in an isolated yeast and human cells, respectively. The function and composition of many of ubiquitin complexes is neither taught by the specification nor is known in the art. Thus, the scope of the claims includes numerous structural variants, and the genera of components are highly variant because a significant number of structural differences between genus members is permitted. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being ubiquitin ligase. The general knowledge and level of skill in the art do not supplement the omitted description because specific guidance is needed on the interaction, if it exists, of various members of the ubiquitin ligase family with various E2 ubiquitin conjugating enzymes and F-box binding proteins. Furthermore, the claims are drawn to a method of use *in vivo* whereas the specification teaches a method of use of an isolated host cell. A method of use *in vivo* reads on a method of use of an entire organism. Given this lack of description of representative species encompassed by the genera of the claims, the specification fails to sufficiently describe the claimed invention

in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-11, 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of Cdc4 and βTrCP hybrids for degradation of polypeptides in yeast and human cells, respectively, does not reasonably provide enablement for a method of use of any hybrid based on any component of ubiquitin ligase, including components of SCF other than Cdc4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Claims 1-11, 14 and 15 are drawn to a method of use of any hybrid polypeptide comprising any ubiquitin protein ligase and a target polypeptide interaction domain in any host cell. This amounts to any hybrid polypeptide comprising peptide structures both naturally-occurring and man-made. "A ubiquitin protein ligase" encompasses proteins or protein complexes of diverse and, in many cases, unknown structure and function. The specification teaches the hybrids based on Cdc4 and its human analog, βTrCP. It should be taken into account that Cdc4 is auto-ubiquitinated by Cdc34p/SCF^{Cdc4p} complex while other components of this complex, Skp1 and Cdc53, as well as components of other ubiquitin ligase complexes are not (see specification, page 127, last sentence). Also unlike Cdc4p, Sic1p degradation is triggered by Cdc28p-dependent phosphorylation (page 131).

The specification does not support the broad scope of the claims because of the following.

Despite knowledge in the art to produce hybrid proteins, the specification fails to provide guidance as to the composition and structure and function of components of other ubiquitin ligases that can be used in the claimed method other than Cdc4 and its human homolog. The specification provides insufficient guidance as to which of the

essentially infinite possible choices is likely to be successful. The specification teaches the use of Cdc4/βTrCP based hybrids in a host cell naturally containing other components of a ubiquitin ligase complex. The hybrid is cell specific, i.e., Cdc4 is used in yeast cells and βTrCP is used in human cells. It is unknown whether the method can be used in a bacterial cell, for example. The specification does not teach the method as applied for degradation of a polypeptide in a live organism, nor is this taught or predicable from the art. Regarding claim 11, the specification does not teach how to use Skp1 or a cullin polypeptide in the requisite hybrid, particularly taken into account the teachings that Cdc4p is "the only short-lived component of the Cdc34p/SCF^{Cdc4p} complex" (page 127, last sentence). Regarding claim 14, the specification does not teach how to use a hybrid comprising E7 and LTP and a second component other than Cdc4.

Therefore, one of ordinary skill in the art would require guidance, in order to degrade a polypeptide by using any hybrid in any cell other than a hybrid based on Cdc4 and βTrCP in yeast and human host cell, respectively, in a manner reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation ""said ubiquitin protein ligase polypeptide-target polypeptide interaction domain hybrid" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 is drawn to the E3 ubiquitin protein ligase which is "an SCF polypeptide". It is confusing because SCF is a complex, no component of which alone has the E3 ubiquitin protein ligase activity. For the same reason, claim 11 is unclear.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
August 3, 2001